Mastication and oral health in elderly persons with dementia

Weijenberg, R.A.F.

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CHAPTER 1

General introduction

BACKGROUND

Dementia

Dementia is an umbrella term for a group of neurodegenerative conditions that are characterized by one or more of the following: loss of memory function, behavioral problems, mood changes [1], serious (disabling) loss of cognitive function, aphasia (*i.e.,* inability to use and understand language), apraxia (*i.e.,* inability to use and understand motor tasks), and/or agnosia (*i.e.,* inability to use and understand objects)[2]. Some of the more common types of dementia are Alzheimer's disease (AD), vascular dementia (VaD), fronto-temporal dementia (FTD), and dementia with Lewy bodies (DLB) [1]. AD is the most prevalent type of dementia, and is diagnosed in about 60% of the cases [3]; it is in the top ten (at number 6) of causes of death in the United States of America [4]. VaD is present in about 30% of those diagnosed with 'dementia' [5]. Prevalence of other types of dementia is harder to quantify. For example, FTD mainly has high incidence numbers in persons younger than 65 years old [6] but its prevalence is lower in the elderly, and DLB is diagnosed in about 4%, but percentages as high as 30% have also been reported [7,8]. For both types of dementia, prevalence numbers are increasing, among others due to new criteria [6,8].

Despite some shared characteristics, there are also differences between these dementias, in both underlying pathophysiology and clinical presentation.

- AD patients have a neuropathology characterized by β-amyloid plaques and protein τ tangles [4] in the temporal-parietal and frontal areas of the brain, and also in the hippocampus, entorhinal cortex, and amygdala [9]. Furthermore, they have typical cell death in the hippocampus,

entorhinal cortex, locus coeruleus, and the nucleus basalis of Meynert [9]. Behaviorally and clinically, loss of memory function is most apparent [4].

- VaD is caused by vascular problems, such as strokes (*i.e.,* cerebrovascular accident, CVA; either cerebral hemorrhaging or infarctions) and presents itself with problems in executive functioning (such as planning and inhibition) rather than memory [4] although any brain-region could be affected and thus, the clinical presentation can be very diverse [10].
- FTD patients have cellular damage in the frontal and/or temporal sides of the brain, resulting in personality changes and aphasia [4]. FTD can be divided into three clinical syndromes: a 'frontal' variant, a 'temporal' variant (also known as semantic dementia), and progressive (non-fluent) aphasia [11].
- People who suffer from DLB have accumulations of α-synuclein protein in the cortex, causing visual hallucinations and sleep disturbances [4]. Patients can also show signs of Parkinsonism [12].
- Finally, mixed types (*e.g.,* an AD patient who has had vascular incidents as well) are commonly observed [4].

Whether someone will develop dementia depends on several factors, such as genetic susceptibility, and also on other aspects, known as risk factors. Ageing is one of the main risk factors for dementia [5,13]. This is reflected in the prevalence numbers: worldwide, the prevalence is 0.7–1.9% for persons aged 60–64 years, at 70–74 years this number is increased to 2.2–5.1%, at 80–84 years it is estimated at 7.3–16.4%, and within the group of >90 years old, reports indicate a prevalence of 26.4–79.5% [14]. The prevalence is not equally spread around the globe: it is relatively high in Latin America, low in Asia, and Western Europe leans towards the higher numbers, especially for women [14]. In 2010, about 35.6 million people suffered from dementia worldwide; this number will have almost doubled to 65.7 million in 2030, due to an ageing population [14].

Besides ageing, known risk factors are a low level of education [15] and illiteracy [5]. Other risk factors are functional dependence in activities of daily living (*e.g.,* eating, walking, or dressing oneself) [16], (cardio)vascular risk factors such as hypertension [17,18], and psychiatric disorders such as depression [13]. A mentally and socially inactive lifestyle is a risk factor [19], as well as physical inactivity [20]. Physical activity is known to attenuate the negative effects of stress [21], cardiovascular disease [22], and their interaction [23] on cognition, and also enriches the environment [24]. An enriched environment offers visual, social and somatosensory stimuli, promotes interaction, and has a positive effect on cognitive function [25].

Knowledge about the risk factors for a certain disease may guide research, and may offer chances for the development of new interventions. For example, regular, moderate intense, physical activity (*e.g.,* brisk walking for 30 minutes, 5 times/week) is currently advised for persons of all ages, wanting to prevent (further progression

of) loss of cognition and dementia[26]. One might suggest that mastication is a form of physical activity, because mastication increases heart rate [27-29] and cerebral blood flow [30-32]. Impaired mastication is also a risk factor for dementia, as will be discussed below.

Mastication

Experimental animal studies show that impairing masticatory activity through modified occlusion or diet leads to deficits in cognitive and neurobiological outcomes [33-35]. Some authors even suggest a causal relationship: active mastication might have a positive, preventive action on loss of cognition, whereas disturbed mastication can cause physiological and behavioral deterioration in animals [36]. In human studies, similar correlations have been reported. Having lost 50% or more of the natural dentition, especially at a younger age, has been identified as a risk factor for developing AD [15,37]. A prolonged period of edentulism (>15 years) [38] and tooth loss [39] is related to an increased risk of lower global cognitive performance in healthy elderly [39]. Edentulism is also associated with lower episodic memory in a healthy sample [40]. Low self-reported dental status was correlated with an increased risk for dementia four years later, in community dwelling elderly persons [41]. A negative relationship between higher cognitive functioning (executive function) and the presence of temporomandibular disorders, orofacial pain, and headaches was found in healthy elderly adults wearing a full dental prosthesis, as well as a positive relationship between mandibular performance (*i.e.,* a domain consisting of maximum bite force and mandibular mobility) and episodic memory [42]. Multiple tooth-loss and self-reported chewing difficulties were associated with impairment in global cognitive functioning in a sample comprising both community dwelling and institutionalized elderly persons [43]. In elderly females suffering from dementia, self-reported masticatory function was found to be significantly lower than in matched females without dementia [44]. In sum, these results show that in both animal studies and human studies, a lower masticatory status is associated with lower cognitive function.

There are a few possible underlying physiological mechanisms that might explain this association.

- **Nutrition** – Being able to maintain an adequate diet, in order to achieve a healthy nutritional status, might play a mediating role in the multifactorial relationship between mastication and cognition [45-48], amongst others by facilitating neurogenesis [49].
- **Enriched environment** – Having a better masticatory function is associated with having a larger variety of food-choices [50]. A complex, enriched environment (such as eating a diverse diet with foods of both hard and soft consistency) can facilitate synaptogenesis [51]. An enriched

environment facilitates recovery of spatial learning ability in aged mice after masticatory rehabilitation [52]. The loss of sensory input through the periodontal receptors can cause an impoverished environment through stimulus deprivation [38], which is known to negatively affect cognition [24].

- **Stress** – Impaired mastication might cause stress, or, given that chewing can relieve stress in both humans [53] and animals [54], it might offer a counteractive mechanism for stress, which is lost when mastication is reduced or hardly possible. Regions involved in memory and executive function, such as the hippocampus and prefrontal cortex, respectively, are known for their vulnerability to stress [55].
- **Blood flow** – The link between mastication and cognition could also have its foundation in the cerebral blood flow. Studies show that mastication increases middle cerebral arterial blood flow velocity [56]. Having proper masticatory function may restore cognition after cerebrovascular damage [57], and getting prosthodontic treatment improves brain perfusion, associated with better cognition [58,59].

Deserving special attention is the suffering from (orofacial) pain, as this might also be of influence on the association between masticatory activity and cognition. Pain in general is undertreated in elderly persons suffering from dementia [60]. Loss of physical activity can be a sign of pain, but it can also be a cause of pain, thus creating a vicious circle [61]. Pain assessment is not easy; a combination of both self-report and observation scales is recommended [62]. Pain indicators are: the facial expression (grimace, rapid blinking); vocalization (including heavy breathing); certain body movements; and changes in behavior, *viz.*, socially (withdrawing, acting aggressively), personally (not eating; wandering) and mentally (confusion, crying) [63]. Specific behaviors indicating orofacial pain might be: holding or rubbing the face, touching the sore area, careful (slow and/or small) mandibular movements, changes in appetite, avoiding some typical foods (hard, or cold), and/or resisting oral care [63]. Given the complex interactions of physical activity with cognition, being aware of (orofacial)pain, and treating it adequately, is essential for general and mental health.

Besides these commonly suggested physiological mechanisms that might explain the relationship between mastication and cognition, some others are also mentioned. Inflammation, for example, has been suggested as a physiological mechanism explaining the correlation between oral health and Alzheimer's disease [64], but the loss of teeth might also be indicative of an (early) adverse lifestyle [65]. Others speculate that perhaps a genetic trait makes one prone to pathological ageing, and causes deterioration of both cognition and masticatory function [38]. Which of these underlying mechanisms is appropriate for explaining the association between mastication and cognition is currently not known. Regardless of the underlying mechanism, however, dementia research should not focus solely on physical and

mental functions, such as mastication and cognition; it should also pay attention to the interaction of these measures of health with relevant patient-based outcomes such as quality of life [66,67].

Quality of Life (QoL)

The construct of Quality of Life (QoL) describes a person's well-being [68] and it is considered an important outcome variable for patients suffering from dementia [69]. It includes, amongst others, physical health, absence of pain, cognitive function, mental contentment, and leading a (socially) fulfilling life [70,71]. QoL scores are related to oral health, through mechanisms of choice of food, (mal)nutrition, presence of orofacial pain, and also xerostomia (*i.e.,* a dry mouth) which can limit speech abilities and denture use [72]. QoL can be assessed with rating-scales or questionnaires, for self-rating or by proxies. Interestingly, ratings of QoL can differ between self-rating and a proxy rating [68,73,74]. For example, self-ratings showed an association between lower QoL and loss of cognition [73] and depression [75], whereas proxies associated increased dependency in activities in daily living with lower QoL [73,75]. Some studies suggest that a rater's mood or health status can influence the patient's QoL score [68], although others dispute this finding [75]. In this thesis, QoL was assessed with a proxy-based questionnaire, because this was also suitable for those unable to self-report, due to suffering from severe dementia [76].

Cognition

The Mini Mental State Examination (MMSE) [77] is the most commonly used [78] screening instrument, which measures global cognition through a brief interview that assesses memory, word naming, personal orientation, and visuo-constructive capacities. The common use makes it attractive for research, since it allows for easy comparison with other studies. The term Cognition is defined by the U.S. National Library of Medicine of the National Institutes of Health (NLM-NIH) as: *'Intellectual or mental process whereby an organism becomes aware of or obtains knowledge'.* Cognition can be assessed with neuropsychological tests, such as short screening instruments or extensive collections of complementary tests, often referred to as a test battery. There are many screening tests available, reviewed by Cullen et al. [78]. In this paper, the authors identify six core domains for cognition: 1) attention/working memory, 2) learning and recall, 3) expressive language, 4) visual construction, 5) abstract reasoning, and 6) executive function. Executive function is an umbrella term, and although it is not (yet) clearly defined in literature, there is general consensus that it describes the ability to operate independently, encompassing higher cognitive functions such as set-shifting/cognitive flexibility, inhibition, divided attention, and goal-directed behavior [79,80]. For clinical purposes, using more tests than just one screening instrument is recommended for investigating cognition [78]. In this thesis,

both screening with the MMSE, as well as elaborate neuropsychological testing has been done, in order to obtain both comparable and thorough information. As the main aim was to study the effect of mastication on cognition and quality of life, masticatory performance needed to be qualified, and preferably quantified, as well.

Masticatory performance

Masticatory performance can be assessed subjectively through self-report, objectively through the assessment of 'markers', or through a combination of both [81]. Subjective assessment of masticatory performance, *e.g.,* with questionnaires, can be informative [81], but in elderly persons with (severe) dementia, self-report is most likely unreliable [82]. Therefore, masticatory performance was assessed in this thesis with an objective method. For this purpose, a new mixing ability protocol using two-color chewing gum was created. In this test, participants chewed a piece of two-color gum for 20 seconds, after which it was retrieved and analyzed. Building on previous work [42,83], mandibular mobility was also assessed, which means measuring the maximal voluntary vertical and horizontal movements one can make with their mouth.

The methods described above for assessing QoL, cognition, and mastication were used to assess elderly persons with dementia, which were recruited in several Dutch organized care settings.

Psychogeriatric care facilities in The Netherlands

In The Netherlands, there are several types of organized care settings providing specialized psychogeriatric (PG) care, such as daycare facilities for community dwelling elderly, and residential settings with varying levels of care, *e.g.,* low-medium care, with an open ward policy (in Dutch '*verzorgingshuis*'), or special care units, with closed wards (in Dutch '*verpleeghuis*'). Attending daycare has a positive effect on both the participant and his/her family members [84] and is typically the first step of the 'care-chain'. As the dementia progresses, residential care becomes inevitable, and the elderly person becomes institutionalized. In this thesis, the three types of organized PG care settings have been incorporated. This approach granted a relatively controlled environment, and created the opportunity for cluster matching.

GENERAL AIM

The main aim of this thesis was to investigate the effect of increased masticatory activity on quality of life and cognition in elderly persons with dementia, which was achieved through an oral health care intervention executed by the nursing staff of psychogeriatric care facilities, and through making changes in diet. The oral health

care intervention was done according to the Dutch 'Oral health care Guideline for Older people in Long-term care Institutions' (OGOLI) [85,86].

OUTLINE

Below is an outline of the chapters of this thesis.

Chapter 1

Chapter 1 is the general introduction to this thesis.

Chapter 2

In chapter 2, the possible causal relationship between mastication and dementia was investigated in peer-reviewed reports. First, animal studies are discussed, followed by human studies, including both experimental and observational studies, performed in healthy and clinical samples. Causality is investigated for these associations according to predefined standards.

Chapter 3

As pain, and especially orofacial pain, can influence both mastication and cognition, it is important to be able to adequately recognize this pain in elderly persons suffering from dementia. Literature on this topic is reviewed in chapter 3.

Chapter 4

The work for this thesis is centered around the investigation of the implementation of an intervention to increase masticatory activity, through improving oral health care and changes in diet. The protocol for this randomized clinical trial (RCT), designed as a longitudinal matched-cluster randomized single-blind multicenter study, is presented in chapter 4. A detailed description of the methods and techniques is given.

Chapter 5

In order to measure whether masticatory function improves, tools for measuring performance are needed; tools that are suitable for the population and the scope of the study. Such a tool was not yet available, and so, a new technique was developed, using two-color chewing gum. This tool was tested for sensitivity for change, reliability, and validity, which is described in chapter 5.

Chapter 6

The baseline data from all participants in the RCT study are investigated with linear regression techniques for possible associations between masticatory performance and cognition, which is presented in chapter 6.

Chapter 7

The effects of the intervention in the RCT are investigated in chapter 7, using a mixed analysis of variance. The analysis was done prior to reaching the pre-established endpoint as described in chapter 4, due to concerns with regards to compliance to the planned intervention.

Chapter 8

In chapter 8, a general discussion of the thesis is provided. The implications of the results of this thesis and recommendations for the future are also given.

Summary

Finally, a summary of the thesis is provided, both in English and in Dutch.

REFERENCES

1. Rockwood K., Bouchard R.W., Camicioli R., Leger G. – **Toward a revision of criteria for the dementias**. *Alzheimers.Dement.* 3(4); 428–440, 2007.
2. Chertkow H. – **Diagnosis and treatment of dementia: Introduction. Introducing a series based on the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia**. *CMAJ.* 178(3); 316–321, 2008.
3. Wimo A., Winblad B., Aguero-Torres H., von Strauss E. – **The magnitude of dementia occurrence in the world**. *Alzheimer Dis.Assoc.Disord.* 17(2); 63–67, 2003.
4. Alzheimer's Association – **2013 Alzheimer's Disease Facts and Figures**. *Alzheimer's & Dementia*. 9(2); 1–71, 2013. Washington.
5. Kalaria R.N., Maestre G.E., Arizaga R., Friedland R.P., Galasko D., Hall K., et al. – **Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors**. *Lancet Neurol.* 7(9); 812–826, 2008.
6. Onyike C.U., Diehl-Schmid J. – **The epidemiology of frontotemporal dementia**. *Int.Rev.Psychiatry*. 25(2); 130–137, 2013.
7. Zaccai J., McCracken C., Brayne C. – **A systematic review of prevalence and**

incidence studies of dementia with Lewy bodies. *Age Ageing*. 34(6); 561–566, 2005.

8. Vann Jones S.A., O'Brien J.T. – **The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies**. *Psychol.Med.* 1–11, 25-3-2013.
9. Duke L.M., Kaszniak A.W. – **Executive control functions in degenerative dementias: a comparative review**. *Neuropsychol.Rev.* 10(2); 75–99, 2000.
10. Chui H.C. – **Vascular cognitive impairment: today and tomorrow**. *Alzheimers. Dement.* 2(3); 185–194, 2006.
11. Scherder E.J.A. – **Epidemiology and neuropathology in aging and dementia**. In: *Aging and Dementia-Neuropsychology, motor skills, and pain*. Amsterdam: VU University Press, 2011. p. 9–32.
12. Fereshtehnejad S.M., Religa D., Westman E., Aarsland D., Lokk J., Eriksdotter M. – **Demography, diagnostics, and medication in dementia with Lewy bodies and Parkinson's disease with dementia: data from the Swedish Dementia Quality Registry (SveDem)**. *Neuropsychiatr.Dis.Treat.* 9; 927–935, 2013.
13. Fernandez M.M., Castro F.J., Perez de Las H.S., Mandaluniz L.A., Gordejuela M.M., Zarranz Imirizaldu J.J. – **Risk factors for dementia in the epidemiological study of Munguialde County (Basque Country-Spain)**. *BMC.Neurol.* 8; 39, 2008.
14. Prince M., Bryce R., Albanese E., Wimo A., Ribeiro W., Ferri C.P. – **The global prevalence of dementia: a systematic review and metaanalysis**. *Alzheimers. Dement.* 9(1); 63–75, 2013.
15. Gatz M., Mortimer J.A., Fratiglioni L., Johansson B., Berg S., Reynolds C.A., et al. – **Potentially modifiable risk factors for dementia in identical twins**. *Alzheimers.Dement.* 2(2); 110–117, 2006.
16. Fauth E.B., Schwartz S., Tschanz J.T., Ostbye T., Corcoran C., Norton M.C. – **Baseline disability in activities of daily living predicts dementia risk even after controlling for baseline global cognitive ability and depressive symptoms**. *Int.J.Geriatr.Psychiatry*. 2012.
17. Richard E., Ligthart S.A., Moll van Charante E.P., van Gool W.A. – **Vascular risk factors and dementia – towards prevention strategies**. *Neth.J.Med.* 68(10); 284–290, 2010.
18. Fillit H., Nash D.T., Rundek T., Zuckerman A. – **Cardiovascular risk factors and dementia**. *Am.J.Geriatr.Pharmacother.* 6(2); 100–118, 2008.
19. Carlson M.C., Helms M.J., Steffens D.C., Burke J.R., Potter G.G., Plassman B.L. – **Midlife activity predicts risk of dementia in older male twin pairs**. *Alzheimers.Dement.* 4(5); 324–331, 2008.
20. Churchill J.D., Galvez R., Colcombe S., Swain R.A., Kramer A.F., Greenough W.T. – **Exercise, experience and the aging brain**. *Neurobiol.Aging*. 23(5); 941–955, 2002.

21. Tortosa-Martinez J., Clow A. – **Does physical activity reduce risk for Alzheimer's disease through interaction with the stress neuroendocrine system?** *Stress.* 15(3); 243–261, 2012.
22. Hamer M., Ingle L., Carroll S., Stamatakis E. – **Physical activity and cardiovascular mortality risk: possible protective mechanisms?** *Med.Sci.Sports Exerc.* 44(1); 84–88, 2012.
23. Hamer M. – **Psychosocial stress and cardiovascular disease risk: the role of physical activity**. *Psychosom.Med.* 74(9); 896–903, 2012.
24. Volkers K.M., Scherder E.J. – **Impoverished environment, cognition, aging and dementia**. *Rev.Neurosci.* 22(3); 259–266, 2011.
25. Kraft E. – **Cognitive function, physical activity, and aging: possible biological links and implications for multimodal interventions**. *Neuropsychol.Dev.Cogn B Aging Neuropsychol.Cogn*. 19(1–2); 248–263, 2012.
26. Denkinger M.D., Nikolaus T., Denkinger C., Lukas A. – **Physical activity for the prevention of cognitive decline: current evidence from observational and controlled studies**. *Z.Gerontol.Geriatr.* 45(1); 11–16, 2012.
27. Wilkinson L., Scholey A., Wesnes K. – **Chewing gum selectively improves aspects of memory in healthy volunteers**. *Appetite*. 38(3); 235–236, 2002.
28. Shiba Y., Nitta E., Hirono C., Sugita M., Iwasa Y. – **Evaluation of mastication-induced change in sympatho-vagal balance through spectral analysis of heart rate variability**. *J.Oral Rehabil.* 29(10); 956–960, 2002.
29. Nitta E., Iwasa Y., Sugita M., Hirono C., Shiba Y. – **Role of mastication and swallowing in the control of autonomic nervous activity for heart rate in different postures**. *J.Oral Rehabil.* 30(12); 1209–1215, 2003.
30. Kordass B., Lucas C., Huetzen D., Zimmermann C., Gedrange T., Langner S., et al. – **Functional magnetic resonance imaging of brain activity during chewing and occlusion by natural teeth and occlusal splints**. *Ann.Anat.* 189(4); 371–376, 2007.
31. Ono T., Hasegawa Y., Hori K., Nokubi T., Hamasaki T. – **Task-induced activation and hemispheric dominance in cerebral circulation during gum chewing**. *J.Neurol.* 254(10); 1427–1432, 2007.
32. Hasegawa Y., Ono T., Sakagami J., Hori K., Maeda Y., Hamasaki T., et al. – **Influence of voluntary control of masticatory side and rhythm on cerebral hemodynamics**. *Clin.Oral Investig.* 15(1); 113–118, 2011.
33. Kubo K.Y., Ichihashi Y., Kurata C., Iinuma M., Mori D., Katayama T., et al. – **Masticatory function and cognitive function**. *Okajimas Folia Anat.Jpn.* 87(3); 135–140, 2010.
34. Frota de Almeida M.N., de Siqueira Mendes F.C., Gurgel Felicio A.P., Falsoni M., Ferreira de Andrade M.L., Bento-Torres J., et al. – **Spatial memory decline after masticatory deprivation and aging is associated with altered laminar distribution of CA1 astrocytes**. *BMC.Neurosci.* 13; 23, 2012.

35. Weijenberg R.A., Scherder E.J., Lobbezoo F. – **Mastication for the mind-The relationship between mastication and cognition in ageing and dementia**. *Neurosci.Biobehav.Rev.* 35(3); 483–497, 2011.
36. Ono Y., Yamamoto T., Kubo K.Y., Onozuka M. – **Occlusion and brain function: mastication as a prevention of cognitive dysfunction**. *J.Oral Rehabil.* 37(8); 624–640, 2010.
37. Kondo K., Niino M., Shido K. – **A case-control study of Alzheimer's disease in Japan – significance of life-styles**. *Dementia*. 5(6); 314–326, 1994.
38. Okamoto N., Morikawa M., Okamoto K., Habu N., Iwamoto J., Tomioka K., et al. – **Relationship of tooth loss to mild memory impairment and cognitive impairment: findings from the Fujiwara-kyo study**. *Behav.Brain Funct.* 6; 77, 2010.
39. Syrjala A.M., Ylostalo P., Sulkava R., Knuuttila M. – **Relationship between cognitive impairment and oral health: results of the Health 2000 Health Examination Survey in Finland**. *Acta Odontol.Scand.* 65(2); 103–108, 2007.
40. Bergdahl M., Habib R., Bergdahl J., Nyberg L., Nilsson L.-G. – **Natural teeth and cognitive function in humans**. *Scand.J.of Psychol.* 48(6); 557–565, 2007.
41. Yamamoto T., Kondo K., Hirai H., Nakade M., Aida J., Hirata Y. – **Association between self-reported dental health status and onset of dementia: a 4-year prospective cohort study of older Japanese adults from the Aichi Gerontological Evaluation Study (AGES) Project**. *Psychosom.Med.* 74(3); 241–248, 2012.
42. Scherder E., Posthuma W., Bakker T., Vuijk P.J., Lobbezoo F. – **Functional status of masticatory system, executive function and episodic memory in older persons**. *J.Oral Rehabil.* 35(5); 324–336, 2008.
43. Lexomboon D., Trulsson M., Wardh I., Parker M.G. – **Chewing Ability and Tooth Loss: Association with Cognitive Impairment in an Elderly Population Study**. *J.Am.Geriatr.Soc.* 60; 1951–1956, 4-10-2012.
44. Miura H., Yamasaki K., Kariyasu M., Miura K., Sumi Y. – **Relationship between cognitive function and mastication in elderly females**. *J.Oral Rehabil.* 30(8); 808–811, 2003.
45. Laudisio A., Marzetti E., Pagano F., Bernabei R., Zuccala G. – **Masticatory dysfunction is associated with worse functional ability: a population-based study**. *J.Clin.Periodontol.* 37(2); 113–119, 2010.
46. Roque M., Salva A., Vellas B. – **Malnutrition in community-dwelling adults with dementia (NutriAlz Trial)**. *J.Nutr.Health Aging*. 17(4); 295–299, 2013.
47. Del Parigi A., Panza F., Capurso C., Solfrizzi V. – **Nutritional factors, cognitive decline, and dementia**. *Brain Res.Bull.* 69(1); 1–19, 2006.
48. Okada K., Enoki H., Izawa S., Iguchi A., Kuzuya M. – **Association between masticatory performance and anthropometric measurements and nutritional status in the elderly**. *Geriatr.Gerontol.Int.* 10(1); 56–63, 2010.

49. van Praag H. – **Exercise and the brain: something to chew on**. *Trends Neurosci.* 32(5); 283–290, 2009.
50. Kimura Y., Ogawa H., Yoshihara A., Yamaga T., Takiguchi T., Wada T., et al. – **Evaluation of chewing ability and its relationship with activities of daily living, depression, cognitive status and food intake in the community-dwelling elderly**. *Geriatr.Gerontol.Int.* 21-12-2012.
51. Aoki H., Kimoto K., Hori N., Toyoda M. – **Cell proliferation in the dentate gyrus of rat hippocampus is inhibited by soft diet feeding**. *Gerontology*. 51(6); 369–374, 2005.
52. Mendes F.C., de Almeida M.N., Felicio A.P., Fadel A.C., Silva D.J., Borralho T.G., et al. – **Enriched environment and masticatory activity rehabilitation recover spatial memory decline in aged mice**. *BMC.Neurosci.* 14(1); 63, 2013.
53. Scholey A., Haskell C., Robertson B., Kennedy D., Milne A., Wetherell M. – **Chewing gum alleviates negative mood and reduces cortisol during acute laboratory psychological stress**. *Physiol.Behav.* 97(3–4); 304–312, 2009.
54. Ono Y., Kataoka T., Miyake S., Cheng S.J., Tachibana A., Sasaguri K.I., et al. – **Chewing ameliorates stress-induced suppression of hippocampal long-term potentiation**. *Neuroscience*. 154(4); 1352–1359, 2008.
55. McEwen B.S. – **Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators.** *Eur.J.Pharmacol.* 583(2–3); 174–185, 2008.
56. Hasegawa Y., Ono T., Hori K., Nokubi T. – **Influence of human jaw movement on cerebral blood flow**. *J.Dent.Res.* 86(1); 64–68, 2007.
57. Kawanishi K., Koshino H., Toyoshita Y., Tanaka M., Hirai T. – **Effect of mastication on functional recoveries after permanent middle cerebral artery occlusion in rats**. *J.Stroke Cerebrovasc.Dis.* 19(5); 398–403, 2010.
58. Narita N., Kamiya K., Yamamura K., Kawasaki S., Matsumoto T., Tanaka N. – **Chewing-related prefrontal cortex activation while wearing partial denture prosthesis: pilot study**. *J.Prosthodont.Res.* 53(3); 126–135, 2009.
59. Kimoto K., Ono Y., Tachibana A., Hirano Y., Otsuka T., Ohno A., et al. – **Chewing-induced regional brain activity in edentulous patients who received mandibular implant-supported overdentures: a preliminary report**. *J.Prosthodont.Res.* 55(2); 89–97, 2011.
60. Plooij B., van der Spek K., Scherder E.J. – **Pain medication and global cognitive functioning in dementia patients with painful conditions**. *Drugs Aging*. 29(5); 377–384, 1-5-2012.
61. Plooij B., Scherder E.J., Eggermont L.H. – **Physical inactivity in aging and dementia: a review of its relationship to pain**. *J.Clin.Nurs.* 21(21–22); 3002–3008, 2012.

62. Scherder E.J., Plooij B. – **Assessment and management of pain, with particular emphasis on central neuropathic pain, in moderate to severe dementia**. *Drugs Aging*. 29(9); 701–706, 2012.
63. Lobbezoo F., Weijenberg R.A., Scherder E.J. – **Topical review: orofacial pain in dementia patients. A diagnostic challenge**. *J.Orofac.Pain*. 25(1); 6–14, 2011.
64. Watts A., Crimmins E.M., Gatz M. – **Inflammation as a potential mediator for the association between periodontal disease and Alzheimer's disease**. *Neuropsychiatr.Dis.Treat.* 4(5); 865–876, 2008.
65. Polidori M.C., Nelles G., Pientka L. – **Prevention of dementia: focus on lifestyle**. *Int.J.Alzheimers.Dis.* 2010.
66. Banerjee S., Samsi K., Petrie C.D., Alvir J., Treglia M., Schwam E.M., et al. – **What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia**. *Int.J.Geriatr.Psychiatry*. 24(1); 15–24, 2009.
67. Elsawy B., Higgins K.E. – **The geriatric assessment**. *Am.Fam.Physician*. 83(1); 48–56, 1-1-2011.
68. Schiffczyk C., Romero B., Jonas C., Lahmeyer C., Muller F., Riepe M.W. – **Generic quality of life assessment in dementia patients: a prospective cohort study**. *BMC.Neurol.* 10; 48, 2010.
69. Wetzels R.B., Zuidema S.U., de Jonghe J.F., Verhey F.R., Koopmans R.T. – **Determinants of quality of life in nursing home residents with dementia**. *Dement.Geriatr.Cogn Disord.* 29(3); 189–197, 2010.
70. Ettema T.P., Droes R.M., de Lange J., Ooms M.E., Mellenbergh G.J., Ribbe M.W. – **The concept of quality of life in dementia in the different stages of the disease**. *Int.Psychogeriatr.* 17(3); 353–370, 2005.
71. Lawton M.P. – **Quality of life in Alzheimer disease**. *Alzheimer Dis.Assoc.Disord.* 8 Suppl 3; 138–150, 1994.
72. Kandelman D., Petersen P.E., Ueda H. – **Oral health, general health, and quality of life in older people**. *Spec.Care Dentist.* 28(6); 224–236, 2008.
73. Beerens H.C., Zwakhalen S.M., Verbeek H., Ruwaard D., Hamers J.P. – **Factors associated with quality of life of people with dementia in long-term care facilities: A systematic review**. *Int.J.Nurs.Stud.* 50(9); 1259–1270, 2013.
74. Crespo M., Hornillos C., de Quiros M.B. – **Factors associated with quality of life in dementia patients in long-term care**. *Int.Psychogeriatr.* 25(4); 577–585, 2013.
75. Crespo M., Hornillos C., Gomez M.M. – **Assessing quality of life of nursing home residents with dementia: feasibility and limitations in patients with severe cognitive impairment**. *Int.Psychogeriatr.* 1–9, 10-6-2013.

76. Bouman A.I., Ettema T.P., Wetzels R.B., van Beek A.P., de Lange J., Droes R.M. – **Evaluation of Qualidem: a dementia-specific quality of life instrument for persons with dementia in residential settings; scalability and reliability of subscales in four Dutch field surveys**. *Int.J.Geriatr.Psychiatry*. 26(7); 711–722, 2011.
77. Folstein M.F., Folstein S.E., McHugh P.R. – **"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician**. *J.Psychiatr.Res.* 12(3); 189–198, 1975.
78. Cullen B., O'Neill B., Evans J.J., Coen R.F., Lawlor B.A. – **A review of screening tests for cognitive impairment**. *J.Neurol.Neurosurg.Psychiatry*. 78(8); 790–799, 2007.
79. Scherder E. – **Functional circuits in cognitive aging and Mild Cognitive Impairment**. In: *Aging and Dementia*.Amsterdam: VU University Press, 2011. p. 33–50.
80. Jurado M.B., Rosselli M. – **The elusive nature of executive functions: a review of our current understanding**. *Neuropsychol.Rev.* 17(3); 213–233, 2007.
81. Woda A., Hennequin M., Peyron M.A. – **Mastication in humans: finding a rationale**. *J.Oral Rehabil.* 38(10); 781–784, 2011.
82. Zuluaga D.J., Montoya J.A., Contreras C.I., Herrera R.R. – **Association between oral health, cognitive impairment and oral health-related quality of life**. *Gerodontology.* 29(2); e667–e673, 2012.
83. Lobbezoo F., van Selms M.K., John M.T., Huggins K., Ohrbach R., Visscher C.M., et al. – **Use of the Research Diagnostic Criteria for Temporomandibular Disorders for multinational research: translation efforts and reliability assessments in The Netherlands**. *J.Orofac.Pain*. 19(4); 301–308, 2005.
84. Gustafsdottir M. – **Beneficial care approaches in specialized daycare units for persons with dementia**. *Am.J.Alzheimers.Dis.Other Demen.* 26(3); 240–246, 2011.
85. Nederlandse Vereniging van Verpleeghuisartsen – **Richtlijn mondzorg voor zorgafhankelijke cliënten in verpleeghuizen**. 2007.
86. De Visschere L.M., van der Putten G.J., Vanobbergen J.N., Schols J.M., de Baat C., Dutch Association of Nursing Home Physicians – **An oral health care guideline for institutionalised older people**. *Gerodontology.* 28(4); 307–310, 2011.